Giant Congenital Nevi: A Conceptualization of Patterns

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Patterns in giant congenital nevi are classified as to extent of cellular involvement of the reticular dermis and by the quality of the fibrous matrix. In addition, classifications are influenced by degrees of cellular atypia. Two general categories are defined. In one, the phenomena are relatively independent of those operative at the dermal – epidermal interface. The lesions are characterized as dermal congenital tumorous dysplasias-blastomas. They are subdivided into major, intermediate, and minor categories and into mature and immature variants. In these variants, disparate populations in the patterns of nodules and plaques (lumpy-bumpy variants) qualify as dermal variants of minimal deviation melanoma as seen in the setting of giant congenital nevi. The respective melanomas in this category are small-cell malignant neoplasms (melanoblastomas of infancy and childhood). In a second category in the clinical setting of giant congenital nevus, rare childhood and some adult melanomas of a more common histologic type evolve from lentiginous and junctional components in patterns that recapitulate those of the dysplastic nevus syndrome. The suspicious areas in all categories are evaluated by the same clinical criteria. In the dysplasia -blastoma category, enlarging nodules must be biopsied. The criteria for the evaluation of lesions in the dysplastic nevus syndrome and in the category of minimal deviation melanoma have application to the unstable regions in giant congenital nevi. *J Invest Dermatol 100:300S–312S, 1993*

HISTORICAL PERSPECTIVES (ENCUMBRANCES TO THE INTERPRETATION OF HISTOLOGIC PATTERNS)

Relevance of Neoplasm-Like Phenomena in the Evolution of Common Nevi With rare exceptions, a ''neoplastic'' quality is implicit in conceptualizations of the evolution of nevocytic nevi [1]. For example, in the evolution of small acquired nevi, a phenotypically pluripotent reserve cell is presumed to reside in epithelium. In the ascribed role, it is the progenitor of not only normal epidermal melanocytes but also nevocytes. In the same scheme, nevocytes migrate from the epidermis into the dermis, and the resulting patterns are both organoid and polarized. In this ascribed, directed growth of nevocytes, ''neoplastic'' or ''invasive'' qualities are implicit, and primacy generally is attributed to neurocristic derivatives in the epidermis [2].

In characterizations of the evolution of giant congenital nevi, phenomena that are comparable to those in the evolution of acquired nevi are usually presumed to be operative. Giant congenital nevi are merely larger and display greater cellularity and a wider extension of cells than small congenital or acquired nevi. Such characterizations thus become extensions of the manifest phenomena in the evolution of small acquired nevi.

Characterization of Nevocytic Nevi: Clinical and Histologic Limitations Distinctions between congenital and acquired and small and giant nevocytic nevi are recognized but are not sharply denned. The various criteria for the distinctions between giant and small congenital nevi have mostly emphasized clinical characteristics, but in practice these are both arbitrary and controversial [3]. For the distinctions between congenital and acquired nevi, both size and histologic patterns have been emphasized [4,5]. The imprecision of the morphologic distinctions between small and giant congenital nevi and the wide range of histologic patterns in all congenital nevi have thwarted efforts to distinguish between ''congenital'' and ''acquired'' nevi.

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Nevi and Melanomas: Interrelationships All nevus cells are usually characterized as derivatives of melanocytes [1,2], and a malignancy of similar lineage is characterized as melanoma. This custom finds support in the observation that the neoplastic cells of such malignancies commonly are melanogenic.

In the evolution of the common nevi, precursors at the dermal - epidermal interface have a relationship to both stroma and epithelium. In the evolution of common pre-malignant melanocytic dysplasias and the respective common melanomas, a similar relationship between neoplastic cells and stroma is maintained, but overall patterns are distorted. Conceptually, the distorted patterns can be segregated into tiers (as expressed in patterns of growth), and each tier can be further segregated into grades (as expressed in degrees of atypia) [6,7]. The first tier is clinically characteristic. It is optional but usually represented. Most often it is an acquired (postnatal) malformation and qualifies as an expression of disordered homeostasis. In this context, homeostasis is a form of postnatal growth and is a lifelong process, the end result of disordered homeostasis being expressed morphologically as a dysplasia. In the setting of the dysplastic nevus syndrome [6,8–11] (and comparable sporadic variants), a lesion of the first tier is a genetically unstable locus with a non-obligate potential for progressions to higher tiers, each of which is a variant of melanoma. The lesions of the first tier, if expressed, are precursors of melanoma and are representative of pre-malignant dysplasia or, if associated with a remnant of a common nevus, of atypical nevus. In the grading of pre-malignant melanocytic dysplasias and the related atypical nevi (lesions of the first tier), emphasis is placed primarily on degrees of atypia [9].

The patterns in pre-malignant dysplasias are distortions of those in most nevi and anticipate those in most melanomas. They are easily related to and sequenced with those at the dermal – epidermal interface in radial growth components of most primary melanomas [6]. The shared features of pre-malignant melanocytic dysplasias and most melanomas are markers for sequential relationships [6].

First Neoplastic Tier and Common as Well as Alternate Pathways to Melanoma On the basis of established and generally accepted histologic criteria, the variable patterns in the category of the pre-malignant melanocytic dysplasias are interpretable as cytologic grades of neoplastic

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progression. In the final grade of the first tier, distinctive cytologic and histologic patterns (characterized as a common final pathway) [6,11] anticipate the acquisition of new neoplastic properties and of a potential for a transition from the stage of pre-malignant dysplasia to melanoma (from the first tier to one of several optional tiers). New properties in this neoplastic system that relate to the emergence of melanoma are manifested morphologically by the appearance of a vertical growth component. A vertical growth component has been offered as the most reliable marker for the distinction between pre-malignant dysplasia and melanoma [6,11,12]. The emergence of a population of neoplastic cells with the characteristics of the common final pathway is not the sole pathway to higher tiers. Some dysplasias evolve to higher tiers without expressing the features of the common final pathway. Such lesions are minimal deviation melanomas [6,7,11,13].

Melanoma, Lentiginous, and Junctional Patterns, and the Primary Configuration In characterizations of common melanomas and their evolution, the primacy of precursors in an epithelial domain has been given recognition in the definition of a so-called primary configuration. In this definition (with the additional stipulation that a primary melanoma in a different site has not been previously documented or overlooked), all melanomas with lentiginous and junctional patterns in the epidermis overlying a vertical growth component qualify as primary lesions. This caveat has been questioned in the setting of giant congenital nevi, particularly in infancy and childhood [3,14,15]. In some reported examples of melanoma in giant congenital nevi, a primary configuration has not been identified and has not been a requisite for diagnosis [15].

Giant Congenital Nevi and Melanomas: Statement of Purpose In the setting of congenital nevi, the potential for melanomatous transformation is correlated with size: it is greater in giant than in small variants [16]. The incidence of such transformations in giant congenital nevi has not been established but is generally cited as 4–7%. In statisticians' search for a precise incidence of malignant transformations, the imprecise definitions of the minimal physical limits of giant congenital nevi have been an obstacle.

The current concepts of the evolution of common nevi, prema-lignant melanocytic dysplasias, and common melanomas are of questionable value in the interpretation of some of the patterns in giant congenital nevi. If the common premalignant dysplasias [9], as manifested in the dysplastic nevus syndrome, and the respective common melanomas are selected as models for the conceptualization and interpretation of childhood melanoma in giant congenital nevi, then restrictions will be imposed. There are alternatives. Herein the patterns of giant congenital nevi are analyzed histologically, and the results are conceptualized. The morphologic expressions of cutaneous physiologic and embryologic processes are cited as models for the interpretation of some of the patterns in giant congenital nevi.

FEATURES AND CONCEPTS OF SIGNIFICANCE IN THE CONCEPTUALIZATION OF CONGENITAL NEVI

Anatomic Boundaries The separateness of anatomic zones – including the dermal – epidermal interface, the adventitial dermis [17], the interface between the adventitial dermis (stroma) and the reticular dermis, the reticular dermis, and the interface between the reticular dermis and the subcutaneous fat – is an important aspect of conceptualization. Evaluations include attention to cytologic features, patterns in which nevus cells are aggregated, and the quality and quantity of collagenous tissue in the reticular dermis and in septa of the subcutaneous fat.

Anatomic Boundaries and Acquired Nevi In the characterization of acquired nevi, patterns in the adventitial dermis are emphasized: nevus cells are mostly confined to the adventitial dermis [18]. The adventitial dermis is composed of the papillary dermis and the perifollicular connective sheaths: in the true sense, it is stroma. The adventitia of blood vessels and the sweat gland apparatuses also are stroma but may be distinct from the components of the adventitial dermis.

Anatomic Boundaries and Giant Congenital Nevi In the characterization of giant congenital nevi, patterns in the reticular dermis are emphasized [5]. The reticular dermis is an extension of the retinacula of soft tissue. It is distinguished from stroma by the character and quality of the collagen bundles.

Anatomic Boundaries and Melanomas In the characterization of melanomas, criteria for the recognition of ''minimal deviation melanoma'' provide guidelines that define distinctions among nevi, dysplasias, and melanomas [6,7,11,13]. The criteria include the following.

1. A nodule or plaque of cells with cytologic disparities if the cells in a nodule or plaque are contrasted with the cells of an adjacent nevus or premalignant dysplasia.
2. The cytologic disparities in the population of cells forming the nodule or plaque include greater nuclear and nucleolar size, nuclear -cytoplasmic ratio, and chromatin density.
3. The patterns in the nodule or plaque differ from those of common nevi. They include closely aggregated nests or fascicles or solid sheets of monotonously similar cells.
4. Markers for host immune response are variably represented, in the setting of minimal deviation melanoma arising in giant congenital nevus, they are not a requisite for the diagnosis, and
5. A primary configuration is not a requisite for the diagnosis of minimal deviation melanoma, particularly the dermal variant.

General Concepts of Neoplastic Transformations (Repressive and Derepressive Phenomena) A general definition of types of neoplastic transformation, with no restrictions as to organ system and with emphasis on examples that evolve in stages to a malignancy, is useful in the conceptualization of patterns in giant congenital nevi and related melanomas.

The transformations in the common forms of neoplasia in most organ systems are progressive in nature. In the progressions, organ-specific cytologic and histologic features are relinquished: Grading of the progressions provides a measure of the retained organ-specific characteristics. The progressions of most malignant neoplasms are sequenced in unpredictable tiers and usually include a pre-malignant tier. They are characterized as expressions of derepression of gene functions [12,19,20] and in part are manifested in altered cell cycles. In derepressive neoplastic systems, multiple tiers are accessible and the progressions, if uninterrupted by natural or human intervention, are to higher tiers in an unpredictable genetic and temporal sequence. In early (pre-malignant) lesions, the progressions are non-obligate, and many lesions manifest genetic stability at a level of pre-malignant dysplasia. Degree of atypia may be a rough measure of the potential for progression to higher tiers.

In derepressive neoplastic progressions, the expression of organ-or tissue-specific cellular qualities provides the features whereby one form of neoplasm can be distinguished from others. In higher stages of neoplasia, as specific qualities are progressively relinquished, the neoplastic cells lose their distinguishing characteristics. Their sameness in high-grade neoplasia, irrespective of cell of origin, is given recognition in designations such as anaplastic or undifferentiated carcinoma, anaplastic or undifferentiated large-cell lymphoma, pleomorphic or de-differentiated sarcoma, and undifferentiated malignant neoplasm. The concept of a common final pathway gives recognition to the sameness of high grade neoplasia in a variety of organ systems.

In a second broad category of neoplasia, most common in infancy and childhood, embryonic and fetal patterns are recapitulated. In this category, the maturity of the affected cell line is evaluated by comparisons with patterns in the affected organ during stages of embryonic and fetal development. High grades of neoplasia are manifested in embryonic (immature) patterns. The sameness of neoplastic

cells in high-grade blastomas is given recognition in the designation small-cell undifferentiated malignant neoplasm, and such cells resemble those of early embryos. Conceptually, congenital tumorous dysplasias and blastomas have a repressive quality.

With time, a poorly understood potential for maturation to more adult patterns may be variably and unpredictably expressed. Maturation in an immature lesion, an unpredictable and uncommon parameter, may be spontaneous [21] or may be induced by treatment, such as chemotherapy or radiotherapy.

Maturity and Maturation as Correlated with Repressive Neoplastic Phenomena Both maturity (the pattern of a dysplasia) and maturation (a sequential transformation from an immature or blastomatous pattern to a more mature or dysplastic pattern) as manifested in specific lesions, such as a Wilms' tumor or neuroblastoma, are expressed in histologic patterns [22]. They are evaluated by comparisons with tissue patterns during various stages in the prenatal development of the affected organ system. In the category of neuroblastoma, patterns of maturation include, in ascending order: neuroblastoma, differentiating neuroblastoma, ganglioneuroblastoma, and ganglioneuroma [23]. In the category of renal dysplasias and blastomas, immature lesions are characterized as Wilms' tumor. Mature or differentiated ''benign'' variants are disguised under designations such as nephroblastomatosis, nephrogenic rests, cystic nephroma, cystic partially differentiated nephroblastoma, and even cystic nephroblastoma [24]. In part, the evaluation of the biologic potential of teratomas is based on similar comparisons.

Biologic Implications of Degrees of Immaturity In the repressive genetic phenomena that characterize both congenital dysplasias-blastomas and teratomas, patterns in the affected tissue usually recapitulate those of embryonal and fetal tissue (retrodifferentiation). Embryonal (blastomatous) qualities are related to a potential for malignant behavior. In the neoplastic spectrum of lesions, such as neuroblastoma or Wilms' tumor, some of the lesions are blastomatous, and some are dysplastic in character. The closer the patterns approach normal fetal or adult counterparts, the better the prognosis. The closer the patterns approximate those of embryonal counterparts, the greater the likelihood for malignant behavior.

Evaluations of degrees of maturity, as a measure of prognosis, are of importance in the interpretation of not only congenital dysplasias-blastomas but also of solid teratomas, particularly those of the gonads and, even more particularly, the ovaries (lesions of adolescents and young adults): mature teratomas are dysplasias, and immature teratomas generally are blastomas [25–27]. Immature ovarian teratomas are likely to implant on peritoneal surfaces and are potentially fatal. In prognostications, the immaturity of neural components in solid ovarian teratomas has been identified as an indicator of biologic potential [25]. Immature teratomas and blastomas may differentiate in metastatic sites.

EMBRYOLOGY: PHENOMENA AND SPECULATIONS

Neurocristic Migrants, Phenotypic Options, and Epigenesis The neural crest is a transitory resevoir of remarkably versatile cells. From this resevoir, the native cells emigrate and in rather stereotyped journeys [28] come to reside in and influence the development of a variety of organs and systems [29].

The opinions concerning the nature of neurocristic cells are contrary. Some observers maintain that cells in the neural crest are pre-determined, particularly with regard to melanoblasts [30]. The bulk of evidence favors pluripotency of neural crest cells, at least in their native site of origin and probably until they have selected a residence [31,32]. Some of the observers favor the concept of bipolarity in various sites. In the skin, the polar opposites are Schwann cells and melanocytes [33]. In their migrations, phenotypes may be clustered. Stroma influences both the segregations [34] and the expressions of phenotypes. Fibronectins, laminin, and collagen type IV influence the migrations, and, of note, Schwann cells are a source of all three.

Irrespective of the controversies concerning the nature of neurocristic cells during embryologic development, the evidence for the pluripotency of neurocristic derivatives is found in some studies of neurocristic dysplasias-blastomas [35] and is overwhelming in the patterns that are expressed in post-natal neurocristic dysplasias and malignancies. On this evidence, the pluripotency of neurocristic cells during embryologic development will be the accepted position herein.

During embryologic development, neurocristic migrants, on their arrival in the skin, are phenotypically pluripotent but uncommitted. In selecting the skin as a site of residence, they also commit to a phenotype (epigenesis). The developing dermis is first selected (primary epigenetic site). In primary epigenetic sites (mesenchyme), phenotype is expressed in mesomorphogenesis.

The developing primordial follicles form an avenue for the egress of neurocristic migrants from the mesenchyme into the epithelium. Having selected either primordial follicles or the epidermis as a terminal, the newly arrived immigrants differentiate as melanocytes (secondary epigenesis). As secondary phenotypes, epidermal melanocytes (or their precursors) may be at risk for reversion to the more primitive or primary phenotype, as expressed by neurocristic cells in mesenchyme. In such speculations, the proclivity for nevocytes to revert to a primary

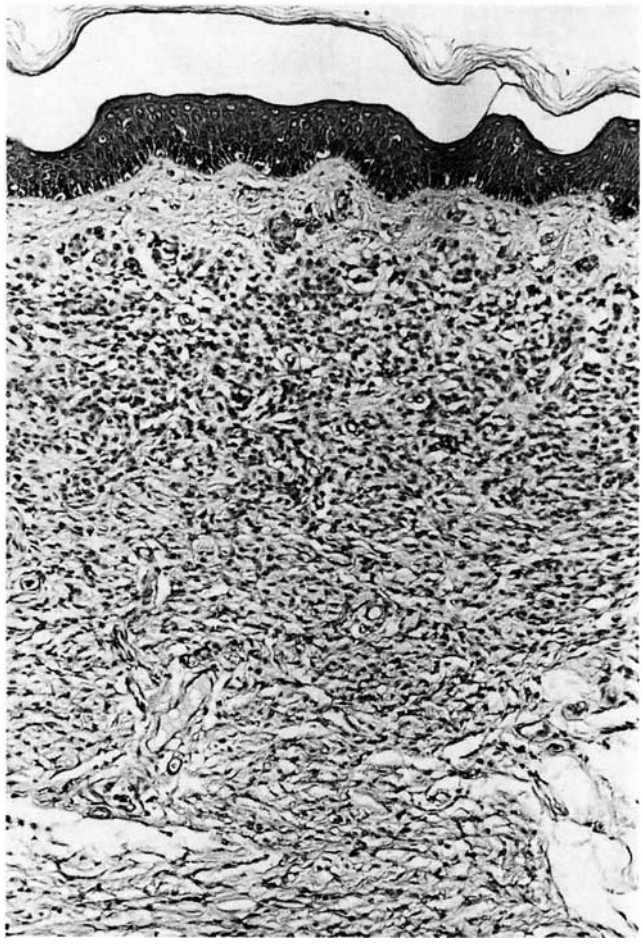

Figure 1. The epidermis and papillary dermis are relatively normal. The reticular dermis is cellular and delicately fibrous. The dysplasia is manifested in the cellularity and the fibrous nature of the reticular dermis. It qualifies as a neuromesenchymal dysplasia. The zone of increased cellularity at the interface between the papillary dermis and the reticular dermis is the zone of phenotypic ambiguity. In this field, the pattern is that of a major, immature congenital nevus.

(ambiguous) phenotype and to return to their primary epigenetic site (dermal mesenchyme) is anticipated.

Phenotypic Diversity of Cutaneous Neurocristic Derivatives Prenatally, three phenotypes are expressed by neurocristic migrants in the developing skin: neurosustentation [31] (with Schwann cells as the definitive expression), melanogenesis [31,33] (with melanocytes as the definitive expression), and mesomorpho-genesis (with particular dermal mesenchymal cells as the definitive expression). These are accurate designations for the functions of non-neoplastic cells in their native domains. On the other hand, melanogenic cells in mesenchyme are an expression of a dysplasia. At the opposite pole, neuroid patterns in the expanded mesenchyme of the papillary dermis of an acquired nevus also are an expression of a dysplasia.

Post-natally, neurocristic migrants in dermal mesenchyme (if such exist) lose their identity in the population of dermal fibrocytes. Their nature occasionally is unmasked in those areas in which some of the dermal cells are also melanogenic (dermal melanocytosis).

Polar Expressions of Phenotypes The divergent differentiation of stroma and retinaculum (including the reticular dermis) may be a manifestation of the reciprocal interplay of neurocristic polar opposites during embryologic development. Melanocytes and Schwann cells are polar opposites. Cells of specialized stromal mesenchyme are intermediates. They may well represent the primal phenotype to which phenotypically committed neurocristic cells revert if removed from a significant epigenetic influence. Nevocytic nevi retain sufficient melanocytic qualities to be classified as melan-ocytic hamartomas. On the other hand, neurofibromas retain sufficient schwannian qualities to be classified as neurosustentacular hamartomas. For both categories, hamartomas function as mesenchyme (neuromesenchyme). The shared qualities in the two categories disclose a common genetic heritage, variably influenced by epigenetic expressions of phenotypes.

Stroma (the adventitial dermis) has ''fetal'' qualities. The retinacula (including the reticular dermis) have ''adult'' qualities. These distinctions are manifested in the preponderant types of collagen in each of the sites and may reflect the opposing effects of dermal and epidermal phenotypes, both of neurocristic derivation. The width of the papillary dermis and the perifollicular connective sheaths may reflect the sphere of influence of melanocytes in arresting the differentiation of a primitive form of mesenchyme. This distinctive mesenchyme is *stroma.*

Neuromesenchyme and Congenital Nevi In congenital nevi, the mesenchymal nature of the dermal component is revealed by the regular spacing of hair follicles: they are not displaced by the population of abnormal cells.

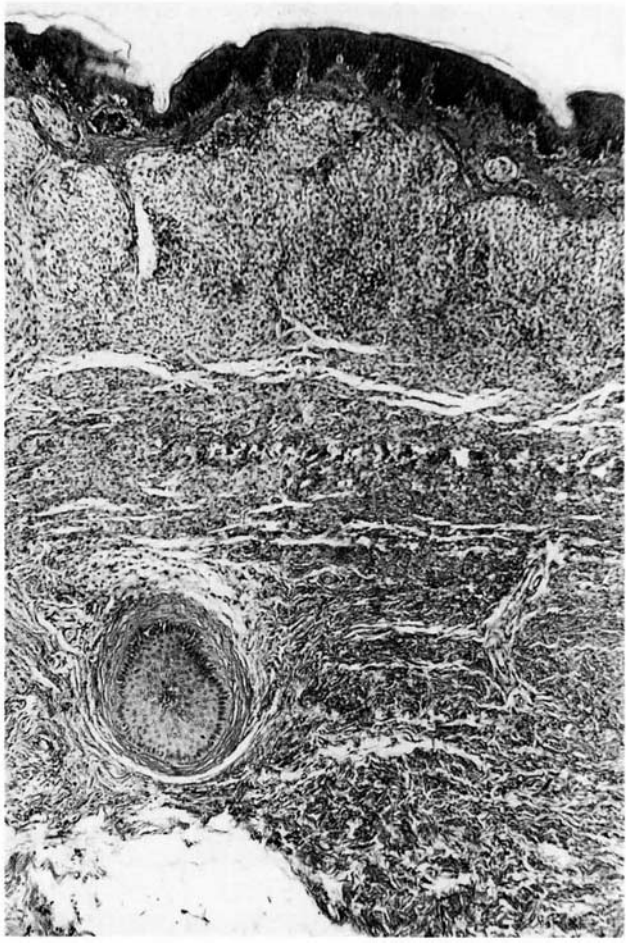

Figure 2. Small, uniform cells form a plaque at the interface between the papillary dermis and the reticular dermis. The papillary dermis and epidermis are relatively uninvolved. The cells extend irregularly into the upper portion of the reticular dermis in the vicinity of a follicle. The lower one-third of the dermis is relatively normal. This is a minor (but giant) mature congenital nevus.

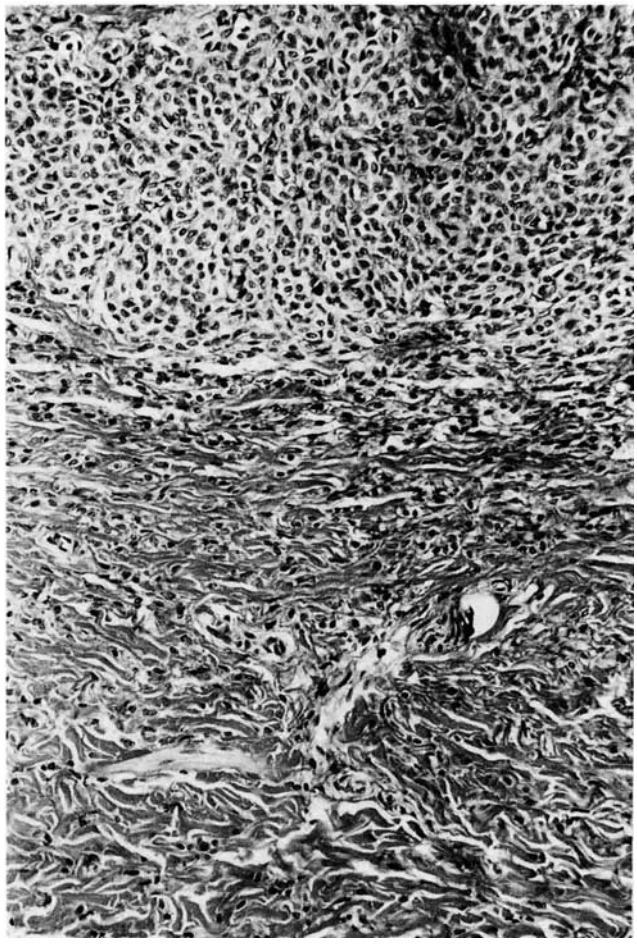

Figure 3. The transition from the cellular zone of phenotypically ambiguous cells (zone of phenotypic ambiguity) to reticular dermis is represented. The collagen bundles of the reticular dermis are fairly well formed and interlace in a normal pattern.

Neuroid patterns and tactoid bodies in an acquired nevus are generally cited as evidence of a phenotypic transformation to a schwannian type of cell (a manifestation of epigenesis: tertiary epigenesis?). As an alternative, the patterns in the papillary dermis of a common nevus may be evidence of a reversion to a primitive mesenchymal phenotype, as expressed in stroma because in them the ''neuroict'' nature of stroma may be revealed.

The columns of nevus cells in the papillary dermis of common acquired nevi project in radiating, neuroid patterns from a nidus of cells at the interface between the papillary dermis and the reticular dermis. Angulated defects or channels are commonly represented in both the columns and nests of nevus cells in the papillary dermis. In these patterns, the embryologic development of the adventitial dermis may be recapitulated. The tendency for nevus cells to cluster in junctional patterns at the tips of rete ridges may relate to phenomena in both embryonic development and adult, cyclic renewal of hair follicles. Nests of pigmented nevus cells in and near the epidermis may be a distorted recapitulation of the melanocytes of an anagen hair bulb. In the polarized descent of nests of nevus cells into the dermis, it is as if the neurocristic framework and the nevus cells (as analogs of matrical melanocytes?) are recapitulating embryologic and physiologic phenomena in the absence of epithelial components.

In senescent nevi, nests of nevus cells are widely spaced in a delicate fibrous matrix. Clustered lipocytes may also be represented. A local hyperplasia of stroma is the end result. A nevus in its senescence thus makes a contribution to the neuromesenchymal stroma.

CRITIQUE

Congenital Nevi and the Reticular Dermis With current popular concepts of the histogenesis of common nevi as guidelines, the patterns in most giant congenital nevi are not manipulable. Some giant congenital nevi are pure dysplasias of the reticular dermis and related retinacula. For such examples, the surface of the skin is smooth, and the papillary dermis and epidermis are uninvolved (Figs 1 and 2). Nevus cells in various patterns and in relation to various skin appendages are distributed in the reticular dermis. They tend to concentrate at the interface between the stroma (adventitial dermis) and the reticular dermis in closely aggregated nests and in solid sheets (Figs 2–4). Markers that document an origin of cells from the dermal – epidermal interface and a migration through the papillary dermis into the reticular dermis are totally lacking.

The changes in the reticular dermis of congenital nevi are not manifested solely in abnormal cellular patterns; for example, collagenous fibrous tissue of the reticular dermis is also abnormal. If the patterns of giant congenital nevi are closely examined, the quality and quantity of fibrous tissue in the reticular dermis is variable. Even in a single example, cellular and fibrous patterns may vary from area to area. In some lesions, or as variations in a lesion, nevus cells are sparsely distributed in the reticular dermis, and the fibrous mat of the reticular dermis is well formed (Figs 2 and 3). In other examples, nevus cells densely populate the dermis, with the greatest concentration of cells at the interface between the reticular dermis and the adventitial dermis: The fibrous matrix of the reticular dermis is deficient (Figs 1, 4, and 5). Often in cellular, poorly

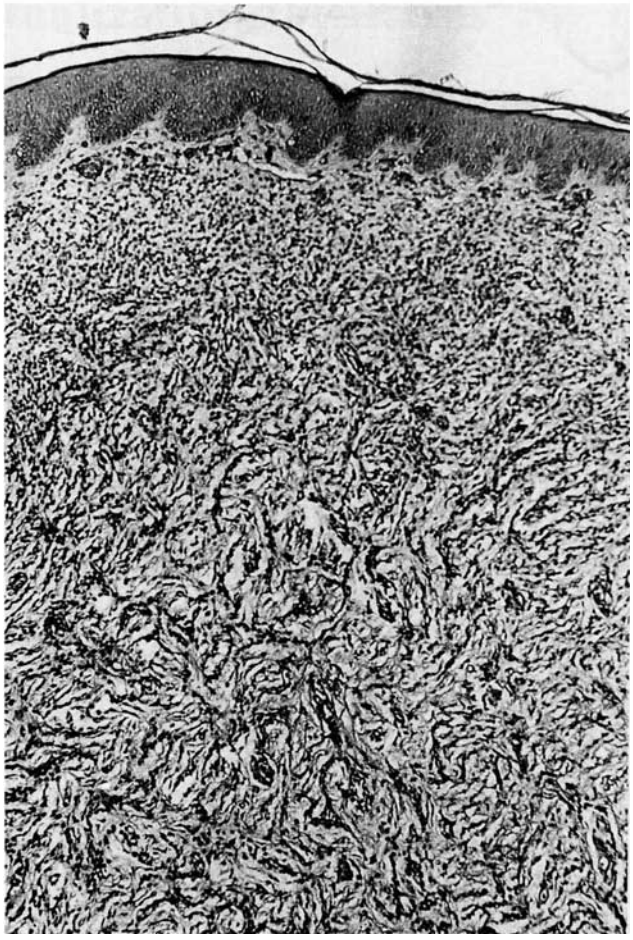

Figure 4. The reticular dermis is fiber poor and cellular. This is a major immature congenital nevus.

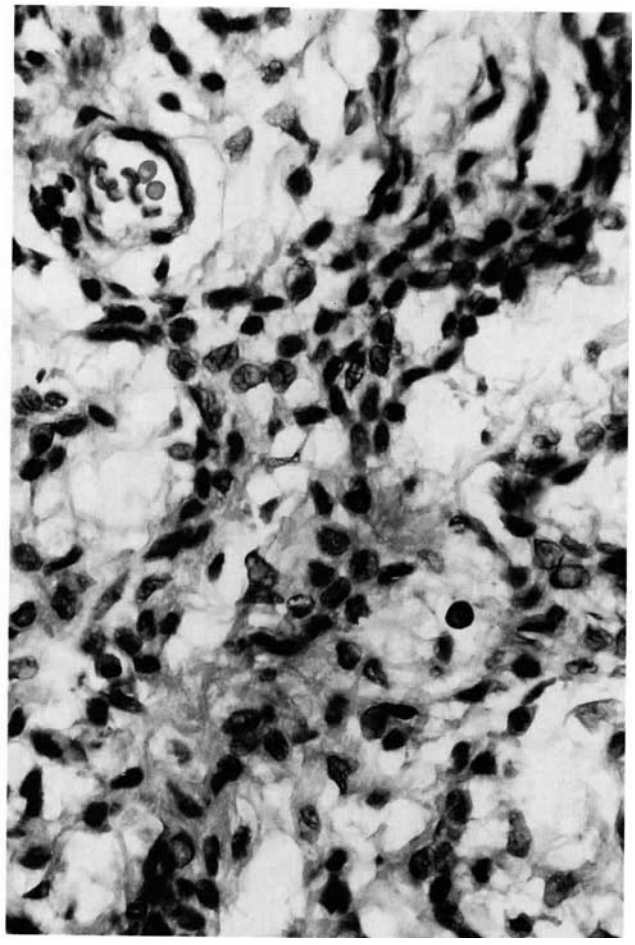

Figure 5. The nevus cells in the reticular dermis are supported by a mucinous, delicate fibrous matrix (same lesion as in Fig 4). The cells are small, with uniform nuclear characteristics.

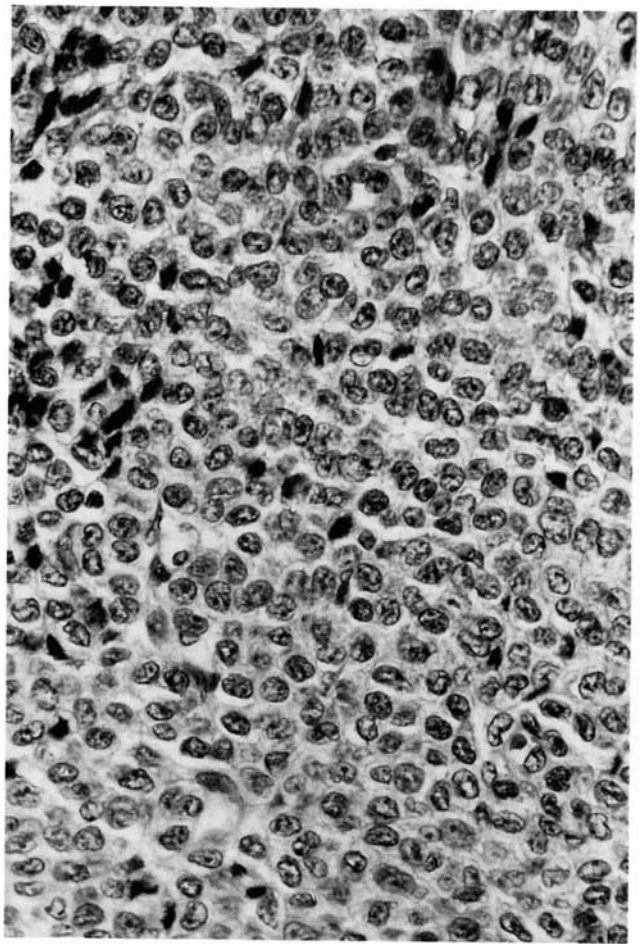

Figure 6. The cells of the zone of phenotypic ambiguity have scanty cytoplasm, slightly enlarged nuclei, and open chromatin patterns. There are occasional mitotic figures.

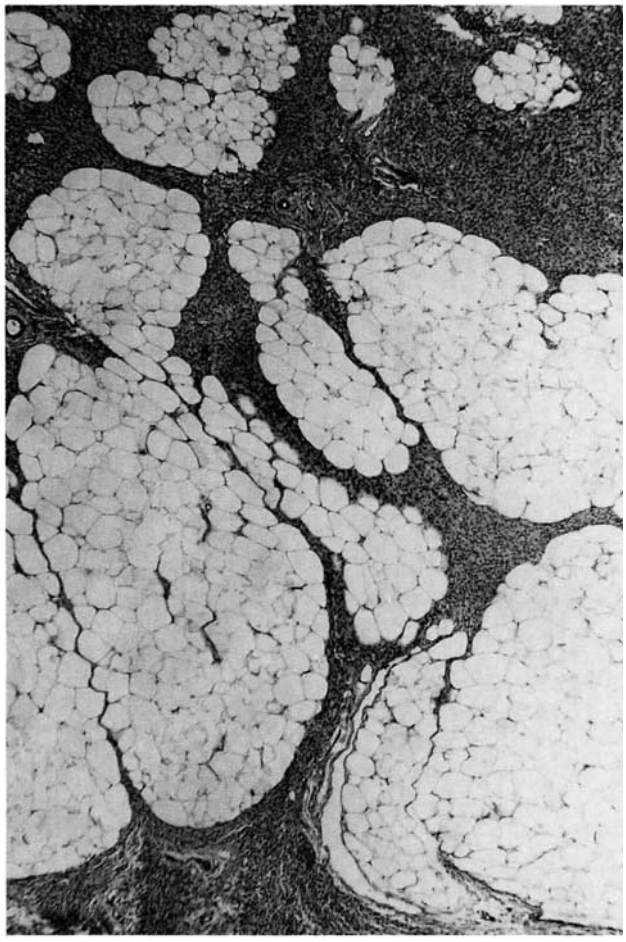

Figure 7. The septa of the subcutis are irregular in size and distribution. Nevus cells involve the septa and extend into the superficial layer of the deep fascia. This is a major immature congenital nevus.

fibrous areas, the nevus cells have scanty cytoplasm with plump, round, somewhat hyperchromatic nuclei and may be associated with mitotic figures: they have atypical qualities (Figs 3 and 6). Cellularity and the quality and quantity of the fibrous mat of the reticular dermis are interrelated.

Generally, for cellular, collagen-poor examples, the fibrous defects and the zones of hypercellularity are most pronounced superficially near the interface between the adventitial dermis (stroma) and the reticular dermis (Figs 1, 4, and 6). In some examples, the dermis is uniformly cellular at all levels and is relatively devoid of stainable collagen bundles (Figs 4 and 5). In some of the more cellular examples, the nevus cells extend along septa and even into the superficial layer of the deep fascia (Fig 7). Rare examples may be associated with components in the deep soft tissue (neurocutaneous melanosis syndrome). In such examples, the patterns of giant congenital nevus and cellular blue nevus often are combined. Patterns that are extraneous to the embryologic development of the skin, such as clustered ganglion cells and tactoid bodies, may be represented (Figs 8 and 9).

Congenital Nevi and Surface Irregularities Some examples of giant congenital nevi are characterized by irregular surface contours (lumpy and bumpy at the surface) (Fig 10). In these areas, dermal nevus cells focally are arranged in solid sheets to form nodules or plaques. In the nodules and plaques, the cells and their nuclei are larger than those in the neighboring nevus: their nuclei are more chromatic, and their nucleoli are enlarged. Mitoses are more common in the cellular zones. The nodules tend to be small (less than a centimeter in diameter). The plaques may be extensive and relatively uniform in vertical dimensions.

Congenital Nevi and Epidermal Lentiginous and Junctional Patterns Many examples of giant congenital nevi are characterized by lentiginous and junctional patterns at the dermal–epidermal interface and by nesting and fascicular patterns in a widened papillary dermis (Figs 11 and 12). They are usually associated with characteristic changes in the reticular dermis, but occasionally the component in the reticular dermis is inconspicuous (Fig 11). These superficial patterns recapitulate those seen in common acquired compound nevi. In some examples, they more closely resemble those of premalignant dysplasias, even with markers for host immune response. The patterns at the dermal-epidermal interface and in the widened papillary dermis usually deviate both architecturally and cytologically from those at the interface between the papillary dermis and the reticular dermis and in the reticular dermis. For some examples, the patterns in the adventitial dermis qualify as minimal deviation melanoma and implicate the second-order phenotypes in the epidermis as the progenitors of the dermal tumor (Fig 13).

SPECULATIONS AND CONCEPTUALIZATIONS

Neuromesenchyme and Dermal Premalignant Dysplasias (Repressive Phenomena) In giant congenital nevi, the patterns in the reticular dermis are difficult to relate to evolutionary phenomena at the dermal –

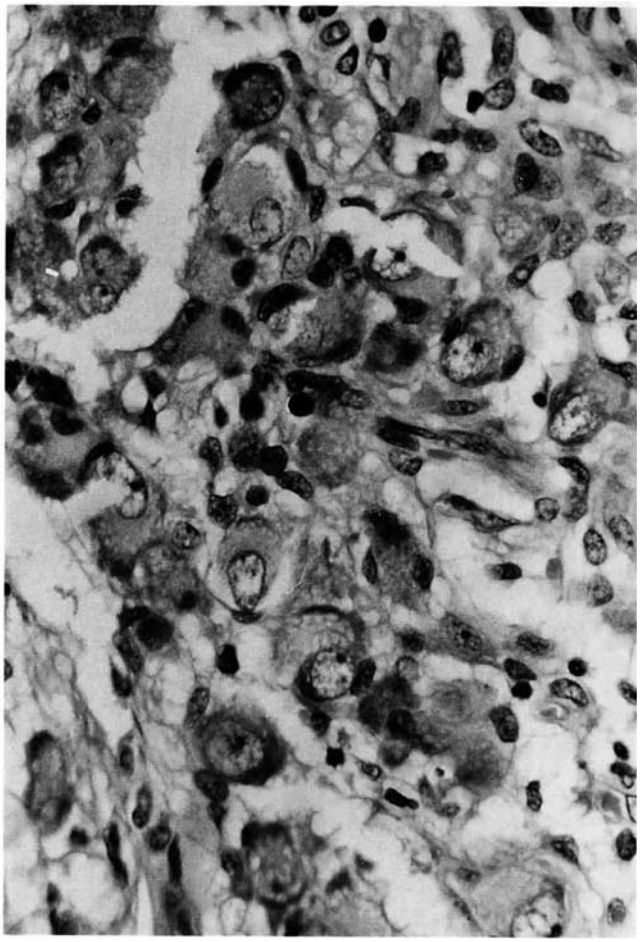

Figure 8. In this portion of a lesion of the neurocutaneous melanosis syndrome, immature ganglion cells are clustered. The dysplasia was extensive and obscured normal anatomic boundaries.

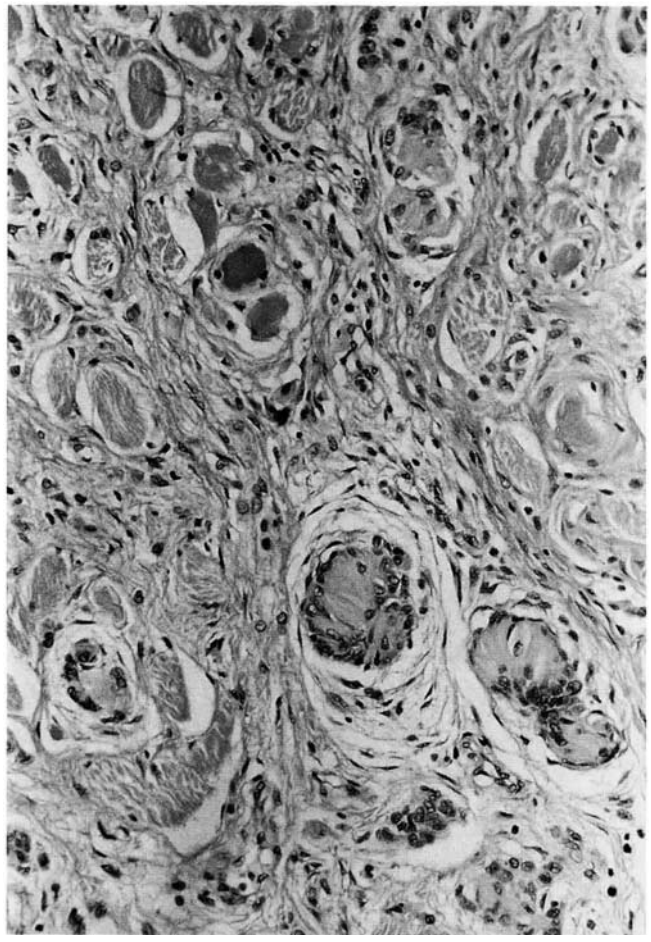

Figure 9. In this area of the same lesion illustrated in Fig 8, a fibrous matrix has entrapped skeletal muscle fibers. Tactoid bodies of the type commonly seen in paraneurofibroma (diffuse neurofibroma or extraneural neurofibroma) are represented.

epidermal interface, particularly in those variants with no components in the epidermis and no alterations of the papillary dermis. For such lesions, the patterns, regardless of preconceived notions, are best characterized as a peculiar mesenchymal dysplasia and are a manifestation of a dysplasia of connective tissue. The alterations in the reticular dermis, if evaluated in combination with an understanding of the neurocristic nature of the respective cells, are expressions of a neuromesenchymal dysplasia [36] and are expressed in degrees of immaturity. The histologic measures of immaturity are cellularity, cytology, mitotic activity, and the quality and quantity of collagenous matrix in the reticular dermis. Mature variants of infancy and childhood are relatively stable lesions. Immature variants in the same periods are unstable and may be associated with nodules and plaques in which the cytologic features, if compared with the patterns in the neighboring skin, are disparate. The cells in the nodules cytologically are more immature than their neighbors.

Melanoblastomas Some melanomas of infancy and childhood in the setting of giant congenital nevus have the qualities of a blastoma [20]. The melanoma cells in such lesions have scanty cytoplasm and plump nuclei with dense, uniformly distributed chromatin (Figs 14–16). They crowd together and are often arranged in patternless sheets. Mitoses and fragments of nuclear debris are common features. The cells may be spindle shaped or round in outline and are supported by a fiber-poor mucinous matrix (Fig 16). Melanoblastomas of infancy and childhood are usually not associated with significant lentiginous and junctional components in the overlying epidermis – they lack a ''primary configuration.'' They are derived from the dermal population of neurocristic effector cells (nevus cells) and incidentally may be melanogenic. If amelanotic, they may be misinterpreted on small biopsy specimens as a small-cell undifferentiated malignant neoplasm (a lesion in the category of blue tumors with small cells) if clinical details are not available to influence the interpretation.

Phenotypic Diversity Multiple and variable phenotypes are commonly expressed in neurocristic dysplasias and neoplasms [20]. In the skin, the phenotypic options include mesomorphogenesis, neurosustentation, and melanogenesis. Mesomorphogenesis in giant congenital nevi is occasionally expressed in mesenchymal patterns, such as cartilage, skeletal muscle, or adipose tissue. In common nevi, clustered lipocytes are the most common expression of mesenchymal differentiation in patterns other than stroma. In respective malignancies, these same potentials may be expressed, often as rhabdomyosarcoma (mesomorphogenesis) (Fig 16).

Spindle cells are common in neurocristic dysplasias of the skin. Patterns of neurosustentation include palisaded nuclei; thin, rigid fascicles of cells; and tactoid bodies (Fig 9). In some giant congenital nevi, the admixture of spindle and round (so-called epithelioid) cells would qualify the respective lesions as variants of combined nevi (congenital combined nevi). Spindle cells and the expression of neurotropism and desmoplasia are interrelated: lentiginous melanomas are peculiarly related to the heteromorphic expressions.

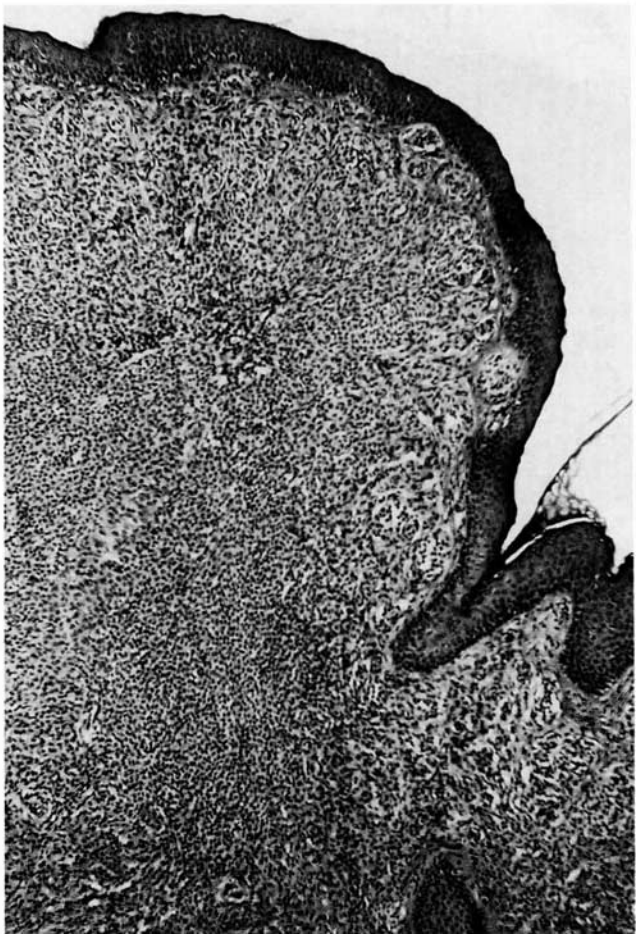

Figure 10. This polypoid lesion is composed of uniform small cells. The lesion is expansile in a background of a major immature congenital nevus. It qualifies as a minimal deviation melanoma of the dermal type as manifested in giant congenital nevus. The pattern relates to the clinical lumpy-bumpy features of some giant congenital nevi.

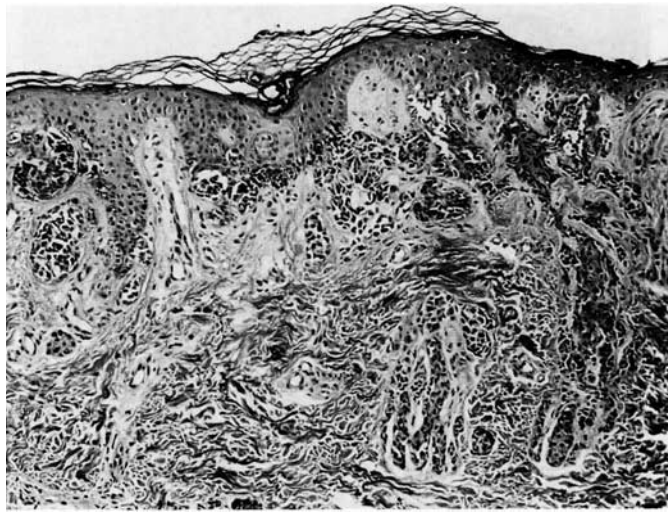

Figure 11. In this congenital nevus, the patterns are lentiginous and junctional at the dermal-epidermal interface. There is cytologic atypia. Some of the fascicles extend into the upper portion of the reticular dermis. The reticular dermis is well formed. This is a congenital nevus that is manifested in relatively pure patterns of ''melanocytic'' differentiation (a dysplasia exclusively affecting second-order phenotypes).

If spindle cells are a crude marker for the expression of neurosustentacular or mesenchymal properties, the concomitant expression of both spindle-cell qualities and melanogenesis reveals the futility of relating dysplastic and neoplastic neurocristic cells to an adult cell of origin. In giant congenital nevi with components in the deep soft tissue (neurocutaneous syndrome), neuroid patterns, ganglion cells, and melanogenic cells may be represented. In the face of such a continuum of phenotypic expressions, an arbitrary assignment restricts the conceptualization of the respective dysplasia.

Lentiginous and Junctional Premalignant Dysplasias (Depressive Phenomena): A Neoplastic Pathway, Separate and Distinct from Dermal Dysplasias (Repressive Phenomena) Lentiginous and junctional patterns in the epidermis and compound patterns with components of similar cells in a widened papillary dermis are common in giant congenital nevi. They are not invariant features. The cells usually are plump, spindle shaped or round, and pigmented. In some examples, lentiginous and junctional components focally have qualities of a premalignant melanocytic dysplasia. These lentiginous, junctional, or compound patterns must be conceptualized separately from the patterns in the reticular dermis. They may be present in infancy and childhood or may become apparent in later life. In infancy and childhood, they are of questionable (unknown) significance. In adults, these patterns may identify lesions at risk for neoplastic progressions and for melanomatous transformations (in common derepressive phenomena).

In giant congenital nevi, lentiginous, junctional, or compound patterns in the reactive superficial unit (the adventitial dermis and the epidermis), and nevus cell patterns in the reticular dermis, are commonly but variably represented in a single lesion and focally are often in continuity. The components in the reticular dermis and also clustered at the interface between the reticular dermis and the papillary dermis genetically have the primal qualities of first-order phenotypes as expressed in mesenchymal patterns. In the patterns at the dermal-epidermal interface, the nevus cell components are progeny of cells that in embryologic development migrated from mesenchyme into epithelium and in the latter site have expressed the option of melanogenesis – they are second-order phenotypes.

These two components of congenital nevi are not directly related in a sequence and one not always the precursor of the other. An expression of a genetic defect prior to the embryonic migration of neurocristic cells into epithelium will affect both mesenchymal and the melanocytic phenotypes. Postnatally, progressions may occur in either or both populations but in adults are more commonly expressed in the epidermal (melanocytic) population. Environmental insults may more readily affect the population in the epidermis (the second-order phenotypes).

Zone of Phenotypic Ambiguity The population of cells at the interface between the papillary dermis and the reticular dermis is a surfeit of phenotypically ambiguous but pluripotent cells (Figs 1–5). As conceptualized herein, they are interpreted as derivatives of the population of cells that influenced the development of the reticular dermis during embryologic development. If associated with lentiginous and junctional components, some of the cells in this zone of phenotypically ambiguous cells may be derivatives of the associate. In migrations of cells from the epidermis into the papillary dermis, those that contact the ambiguous zone may revert to a primitive phenotype and lose their identity.

A reversion in phenotype apparently is less likely in migrations of cells in premalignant dysplasias. In premalignant melanocytic dysplasias, cells in nests in the papillary dermis tend to maintain their melanocytic qualities, even in contact with remnants of a nevus in the ambiguous zone. They are phenotypically distant from common nevus cells and are

Figure 12. Atypical spindle cells extend in nests and fascicles into a widened papillary dermis. The nests and fascicles are compactly aggregated. The fibrous component of the dermis is abnormal and hypercellular. In this congenital nevus, two disparate components are represented. They may not be sequentially related. In the papillary dermis, the patterns are those affecting second-order phenotypes. The close aggregation of fascicles of atypical spindle cells in the papillary dermis qualifies the lesion as a variant of minimal deviation melanoma as manifested in the setting of a giant congenital nevus. In the reticular dermis, the lesion has neuromesenchymal qualities. The collagenous framework is defective. The bundles are thin and too numerous.

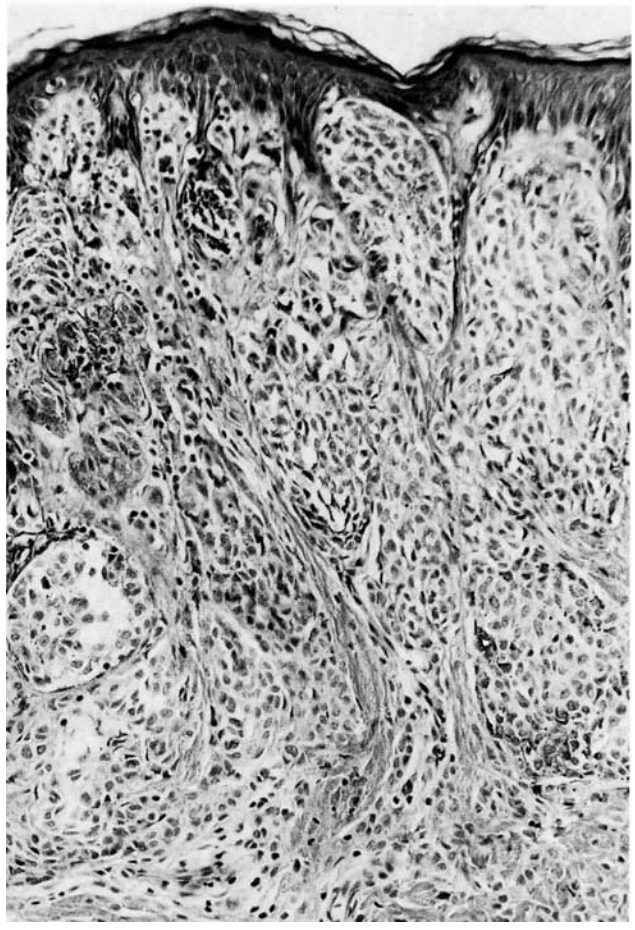

Figure 13. The closely aggregated fascicles in the papillary dermis form a plaque, and the cells are cytologically atypical (same field as in Fig 12). The lesion qualifies as a variant of minimal deviation melanoma in the setting of giant congenital nevus, but the component in the papillary dermis is the progeny of second-order phenotypes (epidermal neurocrisric residents). In this pattern, a process distinct from the phenomena of the dermal neuromesenchymal dysplasia (first-order phenotypes) as manifested in the reticular dermis in Fig 12 is represented.

less likely to revert to the primal type. They may do so and then express alternative phenotypes, such as desmoplasia or neurotropism. In expressing these alternative phenotypes, they may enter vertical growth along a pathway other than the common final one. In following alternative pathways to a higher tier, the resulting neoplasm also qualifies in its early stages of evolution as a minimal deviation variant.

CONCLUSIONS

Congenital Nevi and a Dichotomy of Neoplastic Transformations Herein, histologic patterns have been conceptualized. The concepts relate to the significance of patterns in nevocytic nevi. A dichotomy is defined: a melanocytic component at the dermal -epidermal interface and a neuromesenchymal component at the interface between the papillary dermis and the reticular dermis are representative of separate phenomena and need not be synchronous in origin. The component at the interface between the papillary dermis and the reticular dermis is primal and is a marker for a surfeit of dermal effector cells. The cells at this interface are phenotypically ambiguous. Some of these cells may have been destined to be incorporated in mesenchyme but, as an expression of a dysplasia, replicated in numbers beyond the needs of the developing mesenchyme. In so-called acquired nevi, these cells may be represented to the exclusion of a population in lentiginous and junctional patterns at the dermal – epidermal interface. In common parlance, such lesions are characterized as dermal nevi. By implication, if using currently popular concepts, the precursors of such a lesion evolved initially at the dermal – epidermal interface, but with maturation they all ''dropped'' into the dermis and in the process eradicated all markers for the identification of the site of origin. From an alternative perspective, in many if not all examples of both acquired and congenital nevi, the cells at the interface between the papillary dermis and the reticular dermis initially may be independent of kinetics at the dermal – epidermal interface and do not necessarily provide a marker for migration from epidermis into the dermis. Nests of phenotypically ambiguous cells at the interface between the reticular dermis and the papillary dermis may mark vulnerable sites in which neurocristic derivatives are phenotypically perilous. In such sites, the derivatives at the dermal -epidermal interface may be particularly liable to revert to a more primitive phenotype and migrate into the dermis.

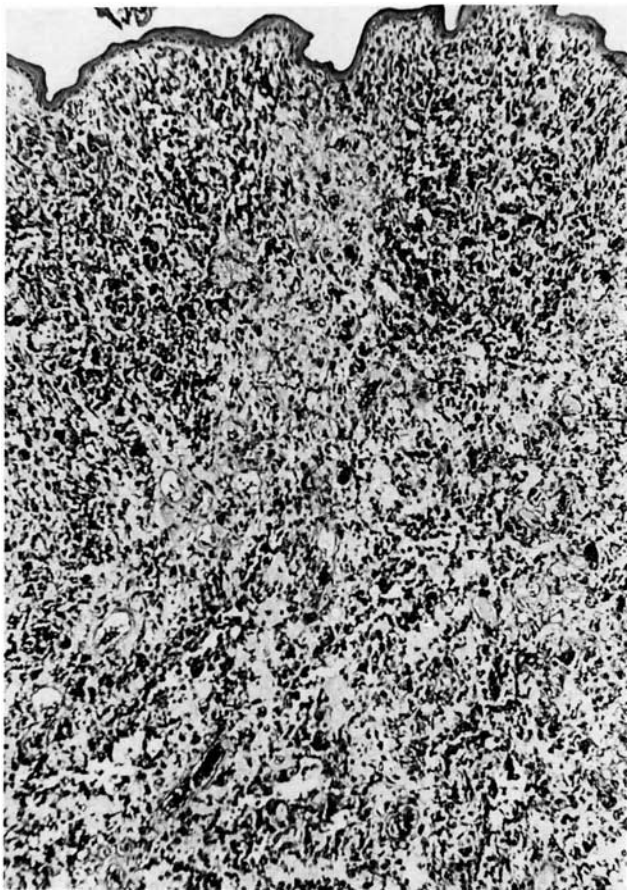

Figure 14. This melanoblastoma of infancy is composed of small, dark cells. It is expansile in the dermis. Lentiginous and junctional patterns are not a feature. The neoplastic cells are supported by a mucinous matrix. The lesion had its origin in a major immature congenital nevus of the interscapular area of an infant. It had metastasized to facial bones within a year of the diagnosis of melanoma.

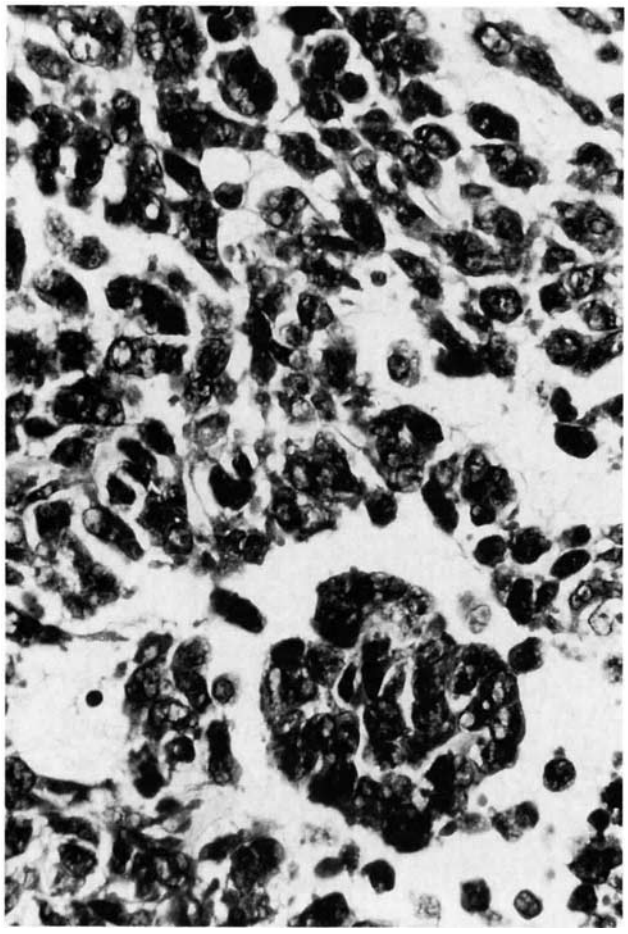

Figure 15. At higher magnification, the blastomatous qualities of the tumor are evident. The matrix is delicate and mucinous. Some of the cells are spindle shaped.

Neuromesenchyme and the Differentiation of Stroma The cells at the interface between components of the dermis have the potential to recapitulate embryonic phenomena; thus, a study of the respective patterns may provide insight into neurocristic contributions to the developing skin.

The columns of nevus cells in the papillary dermis of a common acquired nevus may represent potential perifollicular sheaths. They occasionally cavitate as if in anticipation of a migratory descent of columns of follicular epithelium and related melanocytes (an aberrant expression of both embryonic and physiologic processes) (Figs 17 and 18). In nevocytic nevi, the extremities of rete ridges might be characterized as abortive follicles that have lost the capacity to respond to neuromesenchymal signals. ''Melanocytic'' cells that are clustered in nests at the tips of rete ridges may migrate as an expression of taxis toward the columns. If contact is established, the migrants from the epithelial domain then may revert to an ambiguous phenotype and may relinquish the function of melanogenesis. From this perspective, an acquired nevus is a neuromesenchymal dysplasia expressed in abortive patterns of stromal (including follicular) differentiation. Only neurocristic derivatives are affected. Epithelium does not participate in the dysplasia and is not a component of the dysplasia.

An innate potential for interaction between neuromesenchyme and melanocytes is manifested in distorted patterns in nevi. Neuromesenchyme and melanocytes are polar opposites. In nevi, the distinctions between the two are blurred, and the nevus cells are phenotypically ambiguous.

Characterization of Giant Congenital Nevi (Histologic Correlates) In the designation congenital nevus, a neuromesenchymal dysplasia of the reticular dermis is identified. The designation gives recognition to a histologic characterization that incidentally relates to congenitalness. In this approach, ''congenital'' nevi are divisible into major, intermediate, and minor categories on the basis of the distribution and extent of the dermal component. In major forms, the nevus cells are densely and uniformly distributed throughout the reticular dermis (Figs 1, 4, and 7). They are commonly represented in the retinacula, in skin appendages, and in subintimal zones of muscular vessels. In intermediate variants, the dysplasia tends to spare the lower one-third of the reticular dermis (Figs 2 and 19). In the minor forms, the nevus cells tend to cluster at the interfaces between the adventitial dermis and the reticular dermis. The reticular dermis is relatively normal but somewhat hypercellular (Fig 3). In practice, the intermediate and major forms will also prove to be congenital by clinical history. The minor forms may be ''congenital'' or ''acquired.''

Neuromesenchyme: Maturity and Biologic Potential In the general category of congenital dysplasias-blastomas, gene functions are repressed, and the tissue fails to fully differentiate and mature. The extent and severity of the repression are measured in histologic features, such as

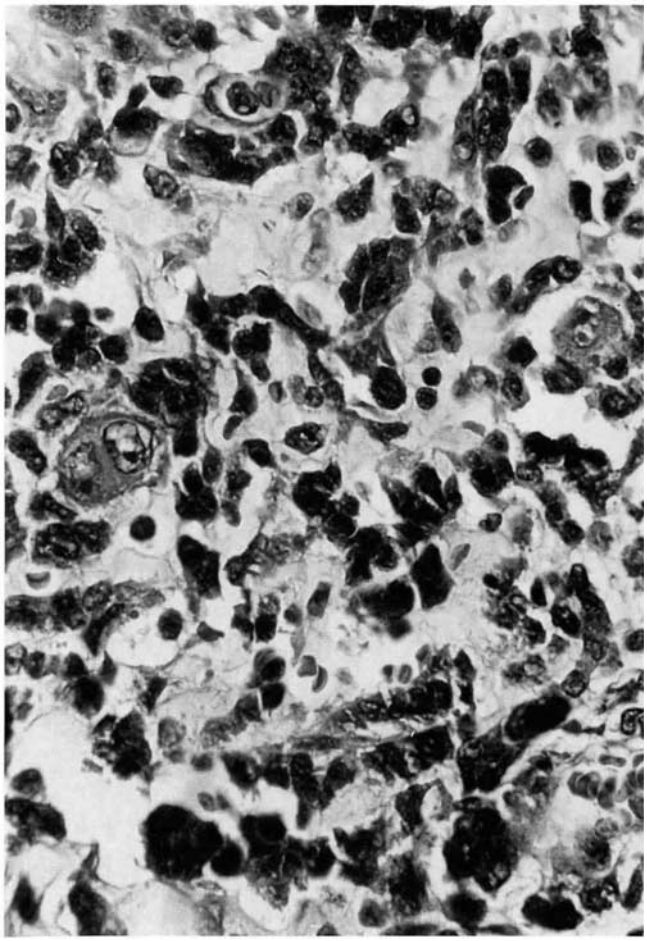

Figure 16. In this portion of a melanoblastoma of infancy (same lesion as in Fig 15), scattered, large epithelioid cells with abundant cytoplasm have the characteristics of rhabdomyoblasts.

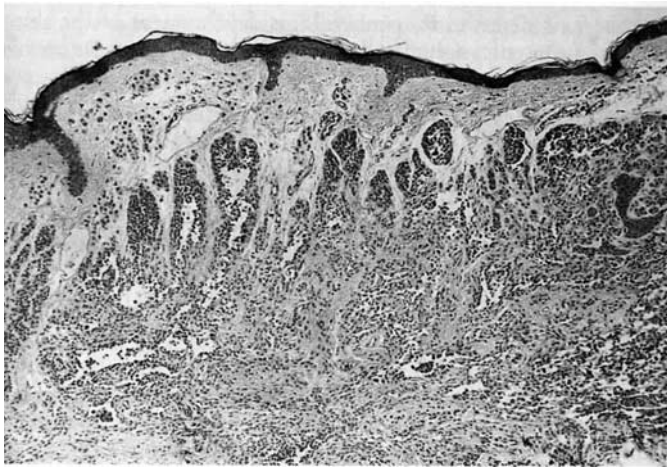

Figure 17. In this common acquired dermal nevus, the nevus cells form regular columns in a widened papillary dermis.

cellularity, maturity, cytologic atypia, and transformation markers [19,37,38]. In congenital nevi, nevus cells are distributed among collagen bundles of the reticular dermis and at anatomic interfaces.

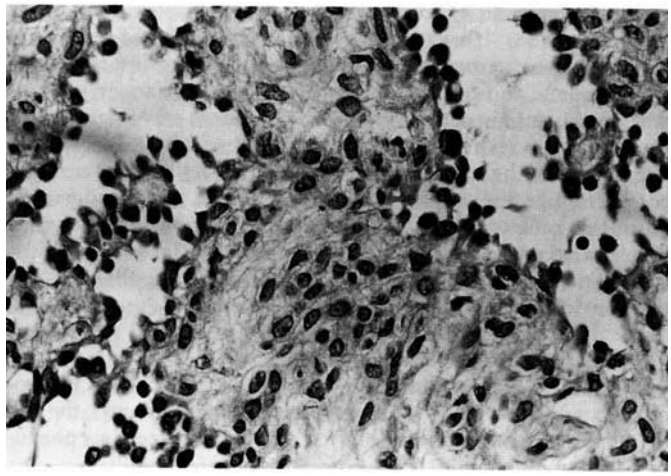

Figure 18. The cavities in the columns of the lesion illustrated in Fig 17 are lined by cuboidal cells. Delicate papillae lined by similar cells project into the cavity.

Cellularity, the quality of the fibrous mat, and cytologic atypia are measures of maturity and of the degree (severity) of dysplasia of the respective nevi. Mature variants are sparsely cellular with a well-formed fibrous component in the reticular dermis. Immature forms are likely to be uniformly cellular (major variants) and to be associated with a deficient fibrous mat. Focally, they may be nodular or plaque-like, with greater immaturity (as judged by cytologic features) in the nodules and plaques than in neighboring components. These plaques and nodules in ''lumpy-bumpy'' severe dysplasias are expressed in disparate cellular patterns (small, uniform, undifferentiated cells in a delicate fibromyxomatous matrix). They are small-cell expansile ''neoplasms'' (they may not be phenotypically related to common melanoma cells [19]). The plaques and nodules usually do not manifest a primary configuration. They may present as one or several small, symmetric nodules that are composed of uniform cells and qualify as the dermal variant of minimal deviation melanoma (Fig 20). They may evolve as invasive, high-grade, small-cell malignant neoplasms (melanoblastoma of infancy and childhood). The cells of melanoblastoma of infancy, if also amelanotic, are difficult to distinguish cytologically from a variety of other blastomas, carcinomas, and sarcomas generally grouped in the category of small-cell undifferentiated malignant neoplasms. In these characterizations of immature major forms, a greater potential for malignant transformation is implicit. The increased risk for melanomatous transformation of giant congenital nevi may not be simply a correlate of size or extent of dermal involvement [19,37,38].

Modulating Effects of Age as Related to the Degree of Histologic Maturity of Giant Congenital Nevi In the conceptual approach as proposed herein, immaturity has prognostic import, but blastomatous transformation is not the only option. An immature giant nevus in the newborn is histologically disturbing. With time, the degree of immaturity in a giant congenital nevus may be favorably modified. If relatively undisturbed, there is an innate but unpredictable potential for differentiation. Quite simply, there are no guides by which the clinician or pathologist can predict the evolution of such a lesion. If conservatism is the chosen path, it must be appreciated that there is also an unmeasured potential for blastomatous transformations. In giant congenital nevi with immaturity and lumps and bumps, the irregularities must be monitored. Areas within such lesions that are clinically unstable should be locally excised. Even careful monitoring will not eliminate the risk for malignant progressions [15]. Immaturity, as a feature of giant congenital nevi, may be directly correlated with the age of the patient at the time of initial

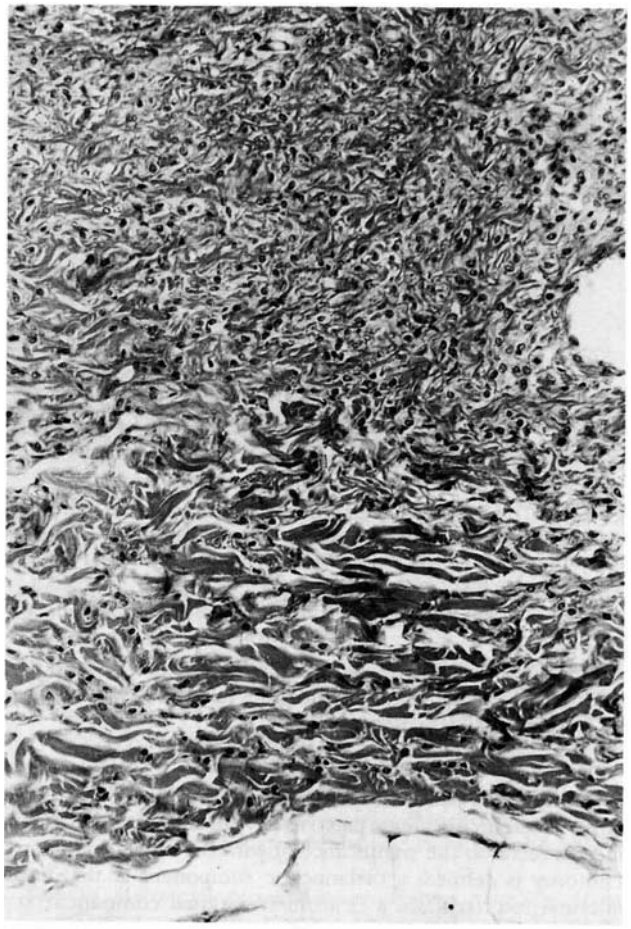

Figure 19. An intermediate pattern in a giant congenital nevus shows a normal pattern of collagen bundles in the lower one-third of the dermis. There is some degree of immaturity in the component in the upper two-thirds of the dermis.

histologic examination. Immaturity may be most evident in the immediate post-natal period. Some examples, if the lesion is not eradicated following the initial histologic interpretation, may mature and differentiate into a less worrisome histologic pattern. The implications of immaturity in the immediate post-natal period are unknown, and the histologic diagnosis of an immature, major variant is not a license for aggressive surgical intervention.

Malignant Transformation in Primary Configurations (Derepression of Gene Functions) In the evolution of giant congenital nevi, the phenomena at the dermal–epidermal interface appear to be independent of those in the reticular dermis, in particular those at the interface between the papillary dermis and the reticular dermis.

The patterns at the dermal – epidermal interface in giant congenital nevi cannot be simply dismissed. They are commonly manifested in lentiginous andjunctional patterns with varying degrees of cytologic atypism. The patterns overlap with those of the melanocytic dysplasias of the dysplastic nevus syndrome. In rare examples, cytologically similar atypical cells form plaques or nodules in a widened papillary dermis in patterns of minimal deviation melanoma (Fig 13).

Two forms of dysplasia, one neuromesenchymal and the other melanocytic, are variably expressed in giant congenital nevi. They commonly coexist in a single lesion. At points of contact, the distinctions between the two populations are lost in a population of phenotypically ambiguous cells. Neoplastic transformations are common in both components. For the ''melanocytic'' component, evolutions are

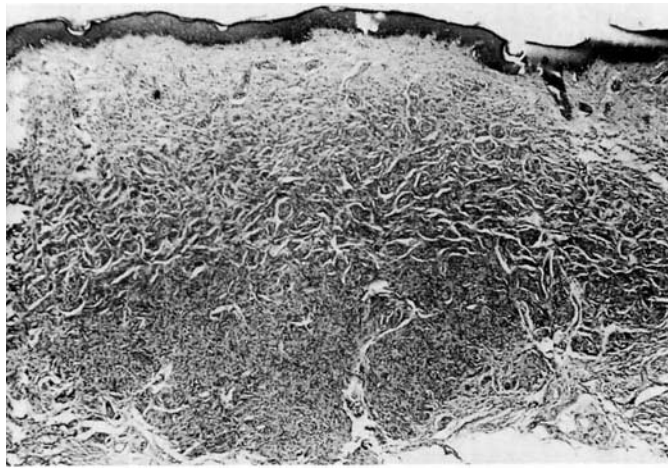

Figure 20. This nodule of disparate cells was represented in the dermis of a major immature congenital nevus and was adjacent to the melanoblastoma of infancy shown in Fig 14–16. It is a dermal variant of minimal deviation melanoma.

de-repressive in patterns that recapitulate those of the dysplastic nevus syndrome. In neoplastic transformations, gene functions are de-repressed, and morphologic features of differentiation are progressively relinquished. Progressions at the dermal-epidermal interface in patterns of the common melanomas are more likely to be late in onset. For the ''neuromesenchymal'' component, evolutions are repressive and in their final expression are blastomatous. The blastomatous lesions are more frequent in infancy and childhood.

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